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09/850,031	05/08/2001	Nobuhisa Shimba	208254US0	9568

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EXAMINER

WEBER, JON P

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 01/15/2003

8

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application N .

09/850,031

Applicant(s)

SHIMBA ET AL.

Examiner

Jon P Weber, Ph.D.

Art Unit

1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 28 October 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) 12-15 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-11 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2,4,5.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

***Status of the Claims***

Claims 1-15 have been presented for examination.

***Election/Restrictions***

Applicant's election with traverse of Group I, claims 1-11 in Paper No. 7, filed 28 October 2002 is acknowledged. The traversal is on the ground(s) that burden has not been met and sufficient reasons have not been provided. This is not found persuasive because 1) sufficient burden was established by the separate classification (MPEP 803) and 2) the mere assertion that insufficient reasons and examples have not been provided is itself insufficient – clear reasons and specific examples were provided at page 2 of Office action of 26 September 2002.

The requirement is still deemed proper and is therefore made FINAL. Claims 12-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7. It is suggested that the nonelected claims be canceled in response to this Office action to expedite prosecution.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific transglutaminase, does not reasonably provide enablement for

Art Unit: 1651

any transglutaminase (TG). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The claims broadly assert that any TG can be used. Only *Streptovercillium mobaraense* transglutaminase MTG is exemplified. In the examples, concentrations of ammonium of 410 mM or more are used. Takagi et al. (1986) report that ammonium is a known inhibitor of TG. They found that >5mM of ammonium sulfate completely inhibits TG incorporation of dansyl cadaverine into casein. Signorini et al. (1991) report that ammonium is a known inhibitor of TG from Silver beet leaves. On the other hand, Muszbek et al. (1985) is representative of references that state that the TG reaction can be monitored by release of the ammonia product. By the well-known principle of microscopic reversibility, if ammonium is the product of the forward reaction, then it is the substrate for the back reaction and should therefore substitute for another amine as an acceptor. This is supported by Soeda et al. (US 5,658,605) who disclose at column 3, lines 5-17 that TG is universally known as the "amine introducing system" for introducing primary amines, ammonia, etc. To reconcile these two conflicting observations, ammonia can serve as an amine donor in the back reaction if and only if its concentration is lower than the amount that inhibits the TG. This is likely very dependent on the particular source of enzyme. Clearly the TGs in the cited art are inadequate to using ammonia easily to label proteins, and certainly not at the concentrations of ammonia asserted in the instant disclosure of over 410 mM. Accordingly, the claims are not commensurate in scope of the enabling disclosure with respect to the source of TG. It would require an undue burden of experimentation to determine additional sources of TG that can be used at the concentrations asserted.

Art Unit: 1651

*Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Iwanij (1977).

Iwanij (1977) discloses the use of transglutaminase to label proteins using [<sup>3</sup>H]putrecine or [<sup>14</sup>C]glycine ethyl ester as the amine donor according to the reaction shown at page 359, column 1. A wide range of soluble and membrane bound proteins were labeled in this manner (e.g., Tables 1-3 and Figs. 3-5).

Claims 1-2 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Russell (US 4,582,794).

Russell (US 4,582,794) discloses the use of transglutaminase to incorporate [<sup>3</sup>H] or [<sup>14</sup>C] labeled polyamines like spermine, spermidine, putrecine, and cadaverine into proteins, e.g. dimethylated casein.

Claims 1 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilbur (1992).

Art Unit: 1651

Wilbur (1992) discloses the use of oxidases and peroxidases to radiohalogenate proteins (page 438, column 1, second full paragraph) by electrophilic substitution at the side chains.

Claims 1-2 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Schieven (US 5,846,998).

Schieven (US 5,846,998) is representative of many references that disclose the use of protein tyrosine kinase and [<sup>32</sup>P]ATP to label proteins on the Tyr hydroxyl with [<sup>32</sup>P] (column 35, lines 27-35).

N.B. Similarly, kinases that phosphorylate Ser and Thr are known to be used for this kind of labeling but were deemed redundant to cite.

Claims 1-2 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Josiah et al. (US 6,146,842).

Josiah et al. (US 6,146,842) disclose using a protein prenyl transferase to incorporate a radioactively labeled prenyl group, e.g., farnesyl or geranylgeranyl, into any protein or peptide with a suitable C-terminal CAAX-motif to which the prenyl group becomes attached (column 5, lines 10-45). Many isotopes can be used (column 5, lines 57-60).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

Art Unit: 1651

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwanij (1977) and Russell (US 4,582,794) in view of Soeda et al. (US 5,658,605).

The teachings of Iwanij (1977) and Russell (US 4,582,794) have been discussed above. Iwanij (1977) and Russell (US 4,582,794) lack incorporating radioactive ammonia into proteins.

Soeda et al. (US 5,658,605) who disclose at column 3, lines 5-17 that TG is universally known as the "amine introducing system" for introducing primary amines, ammonia, etc. into proteins and peptides.

A person of ordinary skill in the art at the time the invention was made would have been motivated to substitute radioactive ammonia as taught by Soeda et al. (US 5,658,605) for radioactive polyamines in the process of labeling proteins as taught by Iwanij (1977) and Russell (US 4,582,794) because Soeda et al. (US 5,658,605) disclose that both ammonia and primary amines can be introduced into proteins by transglutaminase, i.e., they are functional equivalents.

Given that it is known in the art that ammonia is released in the reaction catalyzed by transglutaminase, by microscopic reversibility and Le Chatlier's Principle, it is reasonably expected that excess ammonia can be used to drive the reaction in the back process. Further, if one is willing to accept low yields of isotopically labeled protein, "isotope exchange at equilibrium" guarantees that at least some labeled protein will be formed in the presence of labeled ammonia even at low levels of ammonia.

The reaction catalyzed by transglutaminase is very specific, the incoming amine nucleophile replaces the  $\gamma$ -amino of glutamine on the target protein.

Art Unit: 1651

The selection of pH, particular amounts of substrate, and whether the transglutaminase is  $\text{Ca}^{2+}$ -dependent or  $\text{Ca}^{2+}$ -independent is an arbitrary matter of experimental design choice given that the disclosure does not indicate any criticality to the selection of these result effective variables. They are within the skill of the ordinary artisan to select and optimize for the reaction at hand.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use transglutaminase to incorporate radioactive ammonia into proteins to label the glutamines.

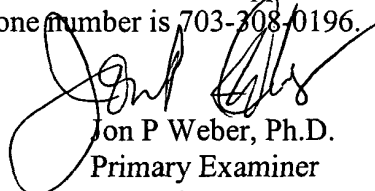
Dutton et al. (1975) provides similar teachings to Iwanij (1977) and Russell (US 4,582,794).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

  
Jon P Weber, Ph.D.  
Primary Examiner  
Art Unit 1651

JPW  
January 10, 2003